Hypoxia Directs Human Extravillous Trophoblast Differentiation in a Hypoxia-Inducible Factor-Dependent Manner.

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Public Summary:
In this manuscript, we provide evidence that a specific type of placental cells, the invasive trophoblast, develops best under low oxygen condition. This is contrary to what has been published before about this cell type, and provide evidence for a specific pathway regulated by oxygen tension which induces differentiation of this invasive trophoblast. This work is significant because it gives tools to study this important cell type in the dish. Without proper function and development of these invasive placental cells, the pregnancy often results in miscarriage or fetal growth problems.

Scientific Abstract:
Villous cytotrophoblasts are epithelial stem cells of the early human placenta, able to differentiate either into syncytiotrophoblasts in floating chorionic villi or extravillous trophoblasts (EVTs) at the anchoring villi. The signaling pathways regulating differentiation into these two lineages are incompletely understood. The bulk of placental growth and development in the first trimester occurs under low oxygen tension. One major mechanism by which oxygen regulates cellular function is through the hypoxia-inducible factor (HIF), a transcription factor complex stabilized under low oxygen tension to mediate cellular responses, including cell fate decisions. HIF is known to play a role in trophoblast differentiation in rodents; however, its role in human trophoblast differentiation is poorly understood. Using RNA profiling of sorted populations of primary first-trimester trophoblasts, we evaluated the first stage of EVT differentiation, the transition from epidermal growth factor receptor+ villous cytotrophoblasts into human leukocyte antigen-G+ proximal column EVT (pcEVT) and identified hypoxia as a major pcEVT-associated pathway. Using primary cytotrophoblasts, we determined that culture in low oxygen directs differentiation preferentially toward human leukocyte antigen-G+ pcEVT, and that an intact HIF complex is required for this process. Finally, using global RNA profiling, we identified integrin-linked kinase and associated cytoskeletal remodeling and adhesion to be among HIF-dependent pcEVT-associated signaling pathways. Taken together, we propose that oxygen regulates EVT differentiation through HIF-dependent modulation of various cell adhesion and morphology-related pathways.